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Enhanced Susceptibility to Kindling by Chlordimeform May Be Mediated by a Local Anesthetic Action

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Enhanced susceptibility to kindling by chlordimeform may be mediated by a local anesthetic action*

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Abstract. The formamidine pesticides amitraz and chlordimeform have recently been shown to be potent proconvulsants (Gilbert 1988). Two main neuroactive properties have been identified as mediators of formamidine neurotoxicity, α-2 adrenergic agonism and local anesthetic actions. These two proposed mechanisms of formamidine action were contrasted using electrical kindling of the amygdala. Male rats were administered 0, 10 and 40 mg/kg of the local anesthetic lidocaine, 0, 0.01 and 0.10 mg/kg of the α-2 adrenergic agonist clonidine or 0, 10 and 30 mg/kg chlordimeform, IP, once per day. After each injection, kindling stimulation was delivered through chronically-implanted electrodes. The high dosage of chlordimeform and both dosages of lidocaine enhanced the rate of kindling development ($\bar{X}$ sessions to stage 5 seizures = 8.6 ± 1.16, 10.15 ± 1.04 and 8.5 ± 0.95, respectively) relative to controls ($\bar{X} = 14.59 \pm 1.36$). Afterdischarge (AD) durations were increased over the first seven sessions by both treatments, but the total cumulative AD did not differ from controls. Clonidine, by contrast, delayed kindling development ($\bar{X} = 27.57 \pm 1.97$) and shortened the mean AD duration over the first seven sessions. These data provide support for a local anesthetic action of chlordimeform and stand in contrast to several recent demonstrations of α-2 activity of formamidines as a primary contributor to formamidine toxicity.

Key words: Seizures – Chlordimeform – Kindling – Amygdala – Lidocaine – Clonidine

High dosages of the formamidine insecticide chlordimeform have been reported to produce hyperactivity, respiratory depression and convulsions (Matsumura and Beeman 1976). A preliminary report by Yim et al. (1977) claimed a progressive increase in behavioral sensitization with repeated administration of low dosages of chlordimeform, a pharmacological kindling effect. Consistent with this preliminary report, we have recently demonstrated formamidine enhancement of susceptibility to convulsions induced by repeated electrical kindling stimulation of the amygdala and dorsal hippocampus (Gilbert 1988). Kindling is an epilepsy model in which seizures are gradually induced in response to repeated, brief, low intensity stimulation of the brain, with limbic sites being the most sensitive. Both behavioral and electrographic parameters of convulsive activity evidence a progressive development and spread of seizure activity which eventually culminates in a fully generalized convulsion (Goddard et al. 1969). Based on the reported biological activity of formamidines (Wang et al. 1975; Benezet et al. 1976; Chinn et al. 1977; Pfister et al. 1977; Maitre et al. 1978; Robinson and Bittle 1979; Bailey et al. 1982; Yim et al. 1978; Hsu and Kakuk 1984; Costa and Murphy 1987; Boyes and Moser 1988), we concluded that the facilitation of kindling was most likely attributable to formamidine α-2 adrenergic or local anesthetic properties (see Gilbert 1988 for discussion).

Lund, Yim, and their colleagues have provided evidence for the local anesthetic action of formamidines in frog sciatic nerve (Pfister et al. 1978) and rabbit heart (Lund et al. 1978, 1979) in vitro, blood pressure, heart rate, and cardiac contractility in dogs (Lund et al. 1978, 1979), and EEG activation in the amygdala of rats (Chinn et al. 1977) in vivo. In these preparations, the local anesthetics procaine and lidocaine were found to mimick the effects of chlordimeform.

In contrast to these reports, evidence from receptor binding studies (Costa and Murphy 1987; Costa et al. 1988), in vitro assays of various types (Robinson 1979; Robinson and Bittle 1979; Hsu and Kakuk 1984; Hsu and Lu 1984; Hsu et al. 1987), and recent in vivo electrophysiological measures (visual and hippocampal field potentials) (Boyes and Moser 1988; Gilbert and Dyer 1988) have provided support for a noradrenergic mechanism of formamidine action. Noradrenergic involvement in convulsions is somewhat equivocal (Callaghan and Schwark 1979; Peterson et al. 1981; Joy et al. 1983; Westerberg et al. 1984), but two reports have recently appeared demonstrating delayed development of amygdala kindling following clonidine, an α-2 adrenergic agonist (Gellman et al. 1987; McIntyre and Guigno 1988). The present experiment was designed to contrast the local anesthetic and α-2 mechanism

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of formamidine action in amygdala kindling by comparing the development of kindled seizures following administration of chlordimeform, clonidine, and the local anesthetic lidocaine.

Methods

Subjects. Adult Long-Evans male hooded rats were obtained from the Charles River Breeding Company, and served as subjects ($N = 89$). Animals were housed individually in plastic cages with wood chip bedding in a colony room maintained on a 12 h/12 h light-dark schedule and a constant room temperature of 24° C. Animals were permitted free access to food and water at all times. At 90–120 days of age animals were anesthetized with 60 mg/kg sodium pentobarbital and stereotaxically implanted with a bipolar electrode in each basolateral amygdala (with the incisor bar set at 3.3 mm below the interaural plane, the coordinates were 2.5 mm posterior to bregma, 4.0 mm lateral to the midline, 7.5 mm ventral to the dura). Electrodes were constructed of twisted strands of nichrome (each strand 125 μm), insulated except for the tips, and crimped onto gold-plated male Amphenol pins. The tips of the electrodes were separated vertically by 0.5 mm. The Amphenol pins were inserted into a 9-pin connector, which was cemented to the animal's skull and anchored with stainless steel screws (0.90 × 1/16 in). The animals were grounded through a screw inserted in the skull overlying the anterior neocortex.

Procedure. One to 2 weeks following surgery, animals were placed in a large Plexiglas testing chamber and connected to the stimulating/recording apparatus via a low-noise shielded cable. The electroencephalogram (EEG) was recorded on a Grass polygraph before and after stimulation in order to record a prestimulation baseline and evoked afterdischarge (AD). An AD was defined as EEG activity, lasting 5 s or longer, consisting of spikes at a frequency of 1 Hz or greater, and of an amplitude of at least four-fold that of the prestimulation baseline. Stimulation consisted of a 1-s train of 60-Hz biphasic squarewaves, each 1 ms in duration, from a Grass S-88 stimulator and PSIU6 constant current converters. AD threshold (ADT) testing began 30 min following chlordimeform (10, 30 mg/kg) or lidocaine (20, 40 mg/kg) administration, and 15 min after clonidine (0.01, 0.10 mg/kg) or saline (0.10, 30 or 40 ml/kg). Salt forms of the drugs obtained from Sigma were dissolved in a 1 ml volume of saline and administered IP. Chlordimeform hydrochloride (technical grade) was a gift from CIBA-Geigy. Dosages and test times for clonidine and chlordimeform were based on those of Boyes and Moser (1988) and chosen to extend previous findings on the seizure properties of chlordimeform (Gilbert 1988). Lidocaine dosages were based on those of Racine et al. (1975) for procaine. ADT was determined by administering a series of stimulations beginning at 20 μA and increasing in 20-μA steps at 1-min intervals until an AD was observed. This intensity was deemed the ADT for that animal. Severity of the behavioral seizure and duration of the evoked AD were recorded following each stimulation. Behavioral seizures were scored according to Racine (1972): stage 1, motor arrest, facial automatisms and chewing; stage 2, chewing and headnodding; stage 3, forelimb clonus contralateral to the side of stimulation; stage 4, rearing and bilateral forelimb clonus; and stage 5, rearing with bilateral clonus and loss of postural control. Following ADT testing, stimulation was delivered once daily at a standard 200 μa intensity until three stage-5 generalized seizures were observed. At this point animals were deemed fully kindled.

Upon completion of the experiment, animals were overdosed with sodium pentobarbital and perfused through the heart with 10% formalin and saline. The brains were removed and prepared for histological analysis using standard techniques. Coronal sections were cut at 60 μm on a freezing microtome, mounted and stained with cresyl violet to verify electrode placement.

Statistical analyses. Data from control subjects did not differ among the treatments and thus were pooled to facilitate description, analysis, and presentation of the results. Data were analyzed using repeated measures ANOVA for kindling rate and AD development. One-way ANOVAs were performed on AD threshold, initial, final (mean AD associated with stage 5 seizures), and total cumulative AD durations. Paired comparisons were assessed using Tukey's test with the $\alpha = 0.05$.

Results

No overt behavioral effects were observed following administration of lidocaine or chlordimeform, although a reddening of the nose and extremities was noted for the latter. The high dose of clonidine produced mild ataxia within 15 min of dosing. As reported previously (Gilbert 1988), and in contrast to Yim et al. (1977), no evidence of behavioral sensitization (in the absence of stimulation) with repeated chlordimeform administration was observed.

Neither clonidine or chlordimeform altered AD thresholds. Lidocaine produced a slight increase in AD threshold which was limited to the low dosage group. AD durations associated with the first kindling session were increased by the high dosages of chlordimeform and lidocaine, and slightly decreased by the low dosage of clonidine. The higher dosage of clonidine, however, failed to alter initial AD durations. The mean AD duration associated with stage 5 seizures did not differ among the treatment groups. These data accompanied by their statistical findings are summarized in Table 1.

Both chlordimeform and lidocaine facilitated the rate of kindling development (see Table 1). The number of sessions required to evoke stage 5 seizures was significantly reduced from the control mean of 14.59 to 8.5 and 8.6 sessions by high dosages of lidocaine and chlordimeform, respectively. Kindling rate was also significantly enhanced by the low dose of lidocaine ($\bar{X} = 10.15$). In contrast, 0.10 mg/kg clonidine retarded the rate of kindling development ($\bar{X} = 27.57$). The low dose clonidine group did not differ from controls ($\bar{X} = 13.83$). An analysis of the number of stimulation sessions associated with each stage of motor seizure is presented in the left panel of Fig. 1. Animals treated with chlordimeform and lidocaine spent significantly fewer sessions in the focal kindling stages (1 and 2) than controls. Interestingly, lidocaine appeared to increase the number of sessions in stage 4. Six animals treated with lidocaine (one from the low dose and the remainder from the high dose group) were observed to experience seizures in the absence of stimulation. These spontaneous seizures occurred following five to ten stimulation sessions and in animals that had previously experienced a stage 4 or 5 kindled seizure. Spontaneous seizures appeared to be pre-

Table 1. Mean ± SE afterdischarge (AD) threshold, durations, and kindling rate following treatment with chlordimeform, lidocaine and clonidine. Results of one-way ANOVAs are indicated, * denotes significant difference from control mean (Tukey, $P<0.05$). Loss of head plugs in clonidine groups decreased sample size (N) for three of the measures

	Dose (mg/kg)	N	AD Threshold (μA)	Initial AD duration (s)	AD duration with stage 5 (s)	Total AD (s)	Sessions to stage 5
Control	0	22	71.82 ± 5.37	10.91 ± 0.71	66.73 ± 5.34	700.95 ± 66.19	14.59 ± 1.36
Chlordimeform	10	9	68.89 ± 8.89	11.78 ± 1.68	76.93 ± 5.64	764.44 ± 73.60	13.22 ± 1.50
	30	10	62.00 ± 6.29	18.40 ± 3.21*	80.65 ± 6.19	565.60 ± 87.89	8.60 ± 1.16*
		ANOVA	$F(2,38)=0.56$, $P>0.5770$	$F(2,38)=5.60$, $P<0.0075$	$F(2,38)=1.58$, $P>0.2193$	$F(2,38)=1.25$, $P>0.2980$	$F(2,38)=4.49$, $P<0.0178$
Lidocaine	20	13	106.15 ± 6.56*	14.85 ± 3.21	77.38 ± 3.90	604.38 ± 51.04	10.15 ± 1.04*
	40	12	85.00 ± 7.02	22.75 ± 5.80*	56.83 ± 6.90	611.42 ± 77.12	8.50 ± 0.95*
		ANOVA	$F(2,44)=7.99$, $P<0.0011$	$F(2,44)=3.87$, $P<0.0284$	$F(2,44)=2.66$, $P>0.0810$	$F(2,44)=0.70$, $P>0.5033$	$F(2,44)=13.83$, $P<0.0001$
Clonidine	0.01	8	67.50 ± 9.21	7.38 ± 0.60*	73.00 ± 14.25 ($N=6$)	587.83 ± 95.33 ($N=6$)	13.83 ± 2.02 ($N=6$)
	0.10	15	85.33 ± 5.33	8.53 ± 0.72	58.64 ± 5.27 ($N=14$)	944.50 ± 69.45* ($N=14$)	27.57 ± 1.97* ($N=14$)
		ANOVA	$F(2,42)=1.97$, $P>0.1516$	$F(2,42)=5.48$, $P<0.0078$	$F(2,39)=0.81$, $P>0.4507$	$F(2,39)=4.48$, $P<0.0178$	$F(2,39)=15.29$, $P<0.0001$

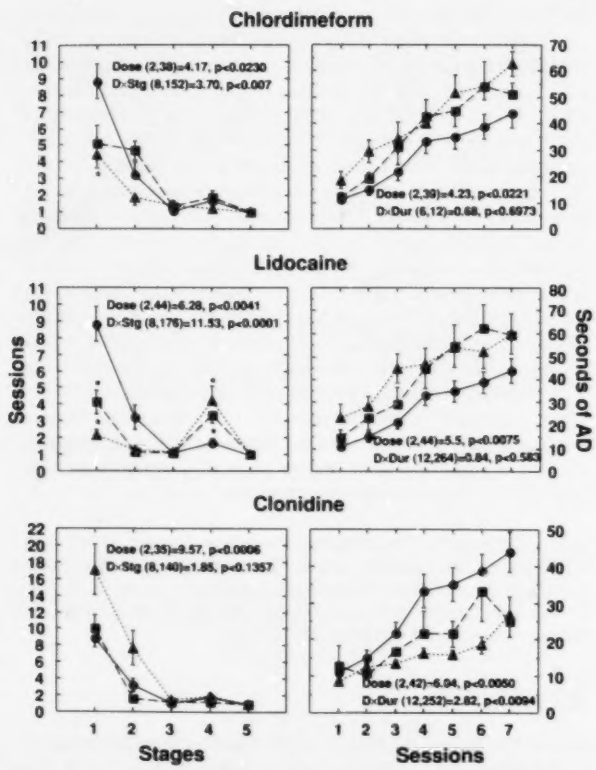

Fig. 1. Mean (±SE) number of sessions in each stage of motor seizure following treatment with chlordimeform, lidocaine and clonidine are shown on the left. Mean (±SE) afterdischarge (AD) duration over the first seven sessions is shown on the right. Results of ANOVA are indicated. *Denotes significant difference from control mean (Tukey, $P<0.05$) following a significant Dose X Stage (*D X Stg*) or Dose X Duration (*D X Dur*) interaction. Chlordimeform: —●— control; ---■--- 10 mg/kg; ---▲--- 30 mg/kg. Lidocaine: —●— control; ---■--- 20 mg/kg; ---▲--- 40 mg/kg. Clonidine: —●— control; ---■--- 0.01 mg/kg; ---▲--- 0.10 mg/kg

cipitated by the administration of lidocaine, as they occurred between 9 and 30 min post-injection.

By contrast, clonidine delayed kindling development. Animals treated with the high dosage of clonidine required more sessions than controls to progress through the focal seizure state (stages 1 and 2) prior to the onset of generalization (stages 3, 4, 5). Three animals treated with clonidine (two from 0.01 and one from 0.10 mg/kg dosage groups) were discarded from the analysis due to dislodgement of the headcap prior to the completion of kindling. Each of these animals, however, had experienced between 16 and 22 ADs, yet had failed to progress beyond stage 2 seizures. An additional four subjects from the high dose group had not progressed beyond stages 1–2 despite 35 ADs. At this point, daily stimulation was continued in the absence of drug administration. Two of these subjects developed stage 5 seizures with an additional 10–25 stimulations, whereas the remaining two failed to show signs of seizure development following an additional 13–21 evoked ADs. A value of 35 was assigned to these subjects for analysis purposes.

The progressive development of AD over the first seven stimulation sessions is presented in the right panel of Fig. 1. Animals treated with chlordimeform and lidocaine experienced significantly longer ADs relative to controls, whereas clonidine-treated animals demonstrated shorter duration ADs. The total cumulative AD over the kindling process, however, failed to differ among controls, lidocaine, chlordimeform, or the low dose clonidine groups. Clonidine, in dosages of 0.10 mg/kg, however, increased the total AD duration during kindling by more than 30% relative to controls (see Table 1).

Discussion

Repeated treatment with the formamidine chlordimeform enhanced the rate of amygdaloid kindling. Seizures were longer in duration and the number of evoked ADs required to produce a generalized seizure state was significantly reduced. These data are in agreement with an earlier report from our laboratory showing enhancement of amygdala

and hippocampal kindling by the formamidines chlordimeform and amitraz. The present experiment extends these findings by providing a dose-response analysis and evidence of chlordimeform-induced enhancement of seizure susceptibility in the absence of overt behavioral signs of toxicity.

A number of parallels were evident in the development of kindling following lidocaine and chlordimeform treatments. Kindling rate was enhanced by both agents, with the predominant acceleration occurring in the focal seizure states. AD duration was increased over several initial sessions yet the total cumulative AD during the kindling process was similar to control values. The lidocaine results are in agreement with and extend earlier findings of procaine-induced enhancement of amygdala kindling (Racine et al. 1975). The facilitation of kindling development induced by chlordimeform and lidocaine was limited to the early stages of kindling, when the seizure is presumed to be focal in nature. Lidocaine, however, increased the number of sessions in stage 4 seizures, a phenomenon not observed in chlordimeform-treated subjects. Lidocaine, as was previously reported for procaine (Racine et al. 1978), came to act as a convulsant in kindled animals (six kindled animals experienced seizures following lidocaine in the absence of stimulation).

The structural similarity between local anesthetic compounds and chlordimeform may account for similar action of the two agents on limbic kindling. The primary action of local anesthetics is to bind to a receptor site part way down the sodium channel once it is activated, and in this manner block nerve conduction (Covino 1987). The somewhat paradoxical finding of seizure activity induced by systemic injections of high dosages of local anesthetics has been attributed to an initial selective block of tonic inhibitory brain mechanisms with a consequent release of excitatory systems (Tanaka and Yamasaki 1966; deJong 1977). The amygdala appears to be particularly sensitive to local anesthetic induction of abnormal EEG spike activity (Prince and Wagman 1966; Wagman et al. 1968). Covino (1987) has suggested that selective uptake by amygdala neurons or enhanced blood flow to this region may account for its vulnerability to local anesthetic-induced spiking. On the other hand, the amygdala/pyriform area may represent a particularly epileptogenic region of the brain (Racine and Burnham 1984; McIntyre 1986; Racine et al. 1986).

In contrast to chlordimeform and lidocaine, clonidine delayed the development of amygdaloid kindling. Animals had briefer electrographic seizures and some failed to develop beyond stage 2 seizures despite 35 stimulations. These findings are in agreement with two recent and independent reports by McIntyre and Guigno (1988) and Gellman et al. (1987). Both of these laboratories provided evidence for postsynaptic α-2 receptor involvement in suppression of kindling development. The possibility exists, however, that chlordimeform, unlike clonidine, demonstrates a higher affinity for autoreceptors on locus coeruleus (LC) neurons, the primary source of forebrain norepinephrine (NE) (Moore and Bloom 1979). A selective interaction with these presynaptic LC α-2 receptors could act to functionally deplete the brain of NE and in this manner lead to facilitation of seizure development. Chemical depletion of NE by 6-OHDA or DSP4 has been shown to facilitate kindling (Arnold et al. 1973; Corcoran 1981; Gellman et al. 1987; McIntyre and Guigno 1988) and exacerbate seizures in other models (Lazarova et al. 1984; Trottier et al. 1988). Future experiments using NE-depleting agents in combination with formamidine treatment may resolve this issue.

In a different limbic preparation (field potentials recorded in the dentate gyrus from single pulses applied to the perforant path), we have demonstrated an increase in hippocampal excitability and reduction in tonic inhibition following treatment with the formamidine amitraz (Gilbert and Dyer 1988). The alterations in hippocampal neuronal activation induced by amitraz could be mimicked by clonidine, offering indirect support for the α-2 adrenergic mechanism of formamidine action. NE has been reported to increase the firing of complex-spike cells (presumably pyramidal cells, the principle cell type of the hippocampal formation). The changes in firing frequency were specific to the α-2 receptor subtype (Pang and Rose 1987). These data are consistent with our findings if α-2 receptors located on dentate granule cells respond in a similar fashion. Preliminary evidence of such action in dentate gyrus has been reported (Pang and Rose 1986). It is possible that the formamidines possess local anesthetic and α-2-adrenergic potential, with these two measures of limbic system physiology (kindling and hippocampal field potentials) tapping each action differentially.

In summary, the present set of experiments suggest that the local anesthetic and not the α-2 adrenergic properties of formamidines contribute primarily to their facilitation of amgydala kindling. This is of particular significance given the convergence of recent data strongly supporting the α-2 mechanism of formamidine action (Costa and Murphy 1987; Boyes and Moser 1988; Costa et al. 1988; Gilbert and Dyer 1988). However, Uemura et al. (1988) using NE-depleted cats, have found evidence for a biphasic action of NE at different stages of kindling development. It was concluded that in the intact animal, NE acts to suppress seizures at the beginning and at the end of the kindling process, but is facilitatory at intermediate stages, prior to full seizure generalization. We have shown that both chlordimeform and lidocaine enhanced kindling rate to a similar degree by reducing the number of sessions in early kindling stages. Clonidine served to suppress kindling development. The lidocaine-induced delay in seizure generalization (from stage 3 to stage 5) and the incidence of spontaneous seizures conspicuously absent from the chlordimeform kindling profile may reflect the joint action of local anesthetic and α-2 activity in formamidine neurotoxicity.

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